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(74) Agents: **BIRD, William, E. et al.**; Bird Goën & Co, Vilvoordsebaan 92, B-3020 Winksele (BE).

(21) International Application Number: PCT/BE00/00118

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99203273.0 6 October 1999 (06.10.1999) EP

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US):
TIGENIX N.V. [BE/BE]; Velpestraat 17, B-3360 Bierbeek
(BE).

Published:

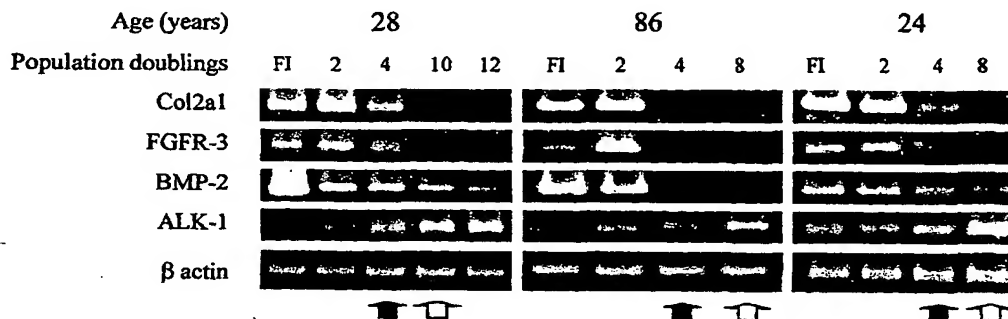
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventors; and

(75) **Inventors/Applicants (for US only):** LUYTEN, Frank [BE/BE]; Baron d'Huartlaan 193, B-1950 Kraainem (BE). DE BARI, Cosimo [IT/BE]; Uzerenmolenstraat 32/127, B-3001 Heverlee (BE). DELL'ACCIO, Francesco [IT/BE]; Uzerenmolenstraat 32/125, B-3001 Heverlee (BE).

(54) Title: IN VIVO ASSAY AND MOLECULAR MARKERS FOR TESTING THE PHENOTYPIC STABILITY OF CELL POPULATIONS, AND SELECTING CELL POPULATIONS FOR AUTOLOGOUS TRANSPLANTATION



(57) Abstract: An *in vivo* assay to measure anchorage-independent growth and phenotypic stability of a certain cell population comprising subcutaneous or intramuscular injection in a mammal of a cell suspension of articular chondrocytes in an iso-osmotic liquid, the same suspension comprising articular chondrocytes in an amount equivalent to at least 1×10^6 chondrocytes as applied to immune-deficient mice. The outcome is linked to molecular markers. The present invention further relates to DNA chips and diagnostic tools comprising the latter to predict the outcome of ACT. Antibodies raised against positive and negative markers of chondrocyte stability can also be used for quality control on the chondrocytes. Therapeutical composition comprising stable chondrocytes are very useful for tissue repair.

WO 01/24833 A2

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 27 June 2001 (27.06.01)	
International application No. PCT/BE00/00118	Applicant's or agent's file reference T1638-PCT
International filing date (day/month/year) 06 October 2000 (06.10.00)	Priority date (day/month/year) 06 October 1999 (06.10.99)
Applicant LUYTEN, Frank et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

18 April 2001 (18.04.01)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BIRD, William, E.
Bird Goën & Co
Vilvoordsebaan 92
B-3020 Winksele
BELGIQUE

Date of mailing (day/month/year) 08 June 2001 (08.06.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference T1638-PCT	
International application No. PCT/BE00/00118	International filing date (day/month/year) 06 October 2000 (06.10.00)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address TIGENIX N.V. Velpestraat 17 B-3360 Bierbeek Belgium	State of Nationality BE	State of Residence BE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input type="checkbox"/> the name	<input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address TIGENIX N.V. Boetsenberg 18 B-3053 Haasrode Belgium	State of Nationality BE	State of Residence BE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input checked="" type="checkbox"/> the designated Offices concerned	
<input checked="" type="checkbox"/> the International Searching Authority	<input type="checkbox"/> the elected Offices concerned	
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Maria Victoria CORTIELLO
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

BIRD, William, E.
Bird Goën & Co
Vilvoordsebaan 92
B-3020 Winksele
BELGIQUE

Date of mailing (day/month/year) 15 April 2002 (15.04.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference T1638-PCT	
International application No. PCT/BE00/00118	International filing date (day/month/year) 06 October 2000 (06.10.00)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input checked="" type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address DELL'ACCIO, Francesco IJzerenmolenstraat 32/125 B-3001 Heverlee Belgium	State of Nationality IT	State of Residence BE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input type="checkbox"/> the name	<input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address DELL'ACCIO, Francesco Celestijnenlaan 3/51 B-3001 Heverlee Belgium	State of Nationality IT	State of Residence BE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ki-Nam HA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT 2001

(PCT Article 36 and Rule 70)

"PO

PCT

Applicant's or agent's file reference T1638-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/BE00/00118	International filing date (day/month/year) 06/10/2000	Priority date (day/month/year) 06/10/1999
International Patent Classification (IPC) or national classification and IPC A61K49/00		
Applicant TIGENIX N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 18/04/2001	Date of completion of this report 18.12.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Langer, A Telephone No. +49 89 2399 7809 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00118

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-31 as originally filed

Claims, No.:

1-28 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

Sequence listing part of the description, pages:

1, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00118

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1-8, 10, 12-17, 20, 21 as to IA.

because:

- ☒ the said international application, or the said claims Nos. 1-8, 10, 12-17, 20, 21 as to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/BE00/00118

1. Statement

Novelty (N)	Yes:	Claims	9, 14-20, 24, 25, 28
	No:	Claims	1-8, 10-13, 21-23, 26, 27
Inventive step (IS)	Yes:	Claims	14-20, 25
	No:	Claims	1-13, 21-24, 26-28
Industrial applicability (IA)	Yes:	Claims	9, 11, 18, 19, 22-28
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item I

Basis of the report

The amendments filed introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

Claim 1 was amended by adding to the in vivo assay the following steps

- b) allowing the formation of cartilaginous tissue
- c) sacrificing the animal
- d) evaluate the formed cartilage histologically for stable, non-vascularised cartilage in vivo
- e) identify positive or negative molecular markers of those isolated or expanded cells evaluated in step d) which form stable, non-vascularised cartilage in vivo.

No basis was provided for the addition of the steps b)-d). The application as originally filed does not disclose an assay comprising all those specific steps. No basis was provided for the inclusion of step b). The cited base for step c) ("freshly isolated cells") is not sufficient, as such cells can also be obtained by biopsy. The cited basis for step d) only refers to the fixation of the cells for histology without specifying the examination, which is to be carried out.

Since all amended claims, which have not only been renumbered or clarified, without any consequences for the evaluation of novelty, refer directly or indirectly to claim 1, the complete set of claims as amended is ignored for evaluation and the preliminary examination report is based on the claims as filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-5, 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). The same applies to **claims 6-8, 10, 12-17, 20** since they may include

subject-matter covered by the provisions of Rule 67.1(iv) PCT.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents. If not indicated otherwise, the relevant passages are those cited in the international search report.

- D1: ERLACHER L ET AL: 'Cartilage-derived morphogenetic proteins and osteogenic protein-1 differentially regulate osteogenesis.' JOURNAL OF BONE AND MINERAL RESEARCH, (1998 MAR) 13 (3) 383-92. , XP002177484
additional relevant passages: column 7, line 24-43
- D2: US-A-5 723 331 (TUBO ROSS A ET AL) 3 March 1998 (1998-03-03) cited in the application
- D3: US-A-5 902 785 (ROSEN VICKI A ET AL) 11 May 1999 (1999-05-11) cited in the application
- D4: WO 98 59035 A (LUYTEN FRANK P ;US HEALTH (US); ERLACHER LUDWIG (US)) 30 December 1998 (1998-12-30) cited in the application
additional relevant passages: p. 4, line 17-36, example 3, claims
- D5: BRADHAM D M ET AL: 'In vivo cartilage formation from growth factor modulated articular chondrocytes.' CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1998 JUL) (352) 239-49. , XP001015830
- D6: QUARTO, RODOLFO ET AL: 'Modulation of commitment, proliferation, and differentiation of chondrogenic cells in defined culture medium' ENDOCRINOLOGY (1997), 138(11), 4966-4976 , XP001015898
additional relevant passages: Fig. 4
- D7: VALCOURT, U. ET AL: 'Different Effects of Bone Morphogenetic Proteins 2, 4, 12, and 13 on the Expression of Cartilage and Bone Markers in the MC615 Chondrocyte Cell Line' EXP. CELL RES. (1999), 251(2), 264-274 , XP001015923
- D8: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STEWART, MATTHEW C. ET AL: 'Phenotypic stability of articular

chondrocytes in vitro: the effects of culture models, bone morphogenetic protein 2, an serum supplementation' retrieved from STN Database accession no. 132:203578 XP002177485 & J. BONE MINER. RES. (2000), 15(1), 166-174 ,

Although document WO 0125402 is not prior art according to R. 64.1(a) PCT, it may in some contracting states be relevant for the evaluation of the present application. In that context it is of particular importance that the priority claimed was found to be only partially valid.

2. Novelty (Art. 33 (2) PCT)

For the evaluation of novelty it has to be taken into account that a product defined by a process cannot be rendered novel by this process since the product itself has to be new.

It is also considered that a document disclosing stable chondrocyte cultures implicitly discloses the features characterising those cultures, e.g. the ratio of positive and negative markers.

The following claims are disclosed by the prior art and therefore lack novelty in terms of Art. 33 (2) PCT:

Claims 1-5 with regard to documents D5 and D6, **claims 6, 7, 10, 11** with regard to documents D1-D8, **claim 8** with regard to document D7, **claims 12, 13, 26** by document D3, **claim 21** by documents D3, D5 and D6, **claims 22, 23** by documents D2, D3, D5, D6, **claim 27** by documents D3, D5, D6, D8.

The technical features of **claims 9, 14-20, 24, 25, 28** are not disclosed by the prior art cited and therefore appear novel in terms of Art. 33 (2) PCT.

3. Inventive Step (Art. 33 (2) PCT)

Claims 1-8, 10-13, 21-23, 26, 27, which are not novel in terms of Art. 33 (2) PCT, also lack inventive step in terms of Art. 33 (3) PCT.

Claims 9, 24 are not inventive in terms of Art. 33 (3) PCT in view of the disclosure

of any of documents D1-D8. The same applies for **claim 28** in view of the disclosure of document D7.

The use of antibodies raised against FGFR-3 and/or ALK-1 in the identification of stable chondrocytes is not indicated by the prior art cited, even though the importance of FGFR-3 in chondrogenesis is known in the art (see description, page 8). **Claims 14-20 and 25** therefore appear inventive in terms of Art. 33 (3) PCT.

4. Industrial Applicability (Art. 33 (4) PCT)

For the assessment of the present **claims 1-8, 10, 12-17, 20, 21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5. Further remarks

In case novelty and inventive step was reestablished for claims 1-13, 21- 24, 26-28, attention is drawn to the fact a problem of unity of the application may arise, since it is at present not apparent which feature could serve as a single general inventive concept for claims 1-28.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference T1638-PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/BE 00/ 00118	International filing date <i>(day/month/year)</i> 06/10/2000	(Earliest) Priority Date <i>(day/month/year)</i> 06/10/1999
Applicant TIGENIX N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

IN VIVO ASSAY FOR TESTING THE PHENOTYPIC STABILITY

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

5 _____

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PC/PSE 00/00118

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERLACHER L ET AL: "Cartilage-derived morphogenetic proteins and osteogenic protein-1 differentially regulate osteogenesis." JOURNAL OF BONE AND MINERAL RESEARCH, (1998 MAR) 13 (3) 383-92. , XP002177484 page 384, column 1 -page 385, column 2	1-28
Y	US 5 723 331 A (TUBO ROSS A ET AL) 3 March 1998 (1998-03-03) cited in the application claims; example 1; table 1	1-28
X	US 5 902 785 A (ROSEN VICKI A ET AL) 11 May 1999 (1999-05-11) cited in the application claims; examples 4,6	1-5,22, 23
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 September 2001

Date of mailing of the international search report

02/10/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

In: International Application No

PCT/SE 00/00118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 59035 A (LUYTEN FRANK P ;US HEALTH (US); ERLACHER LUDWIG (US)) 30 December 1998 (1998-12-30) cited in the application abstract ----	21-23, 27,28
Y	BRADHAM D M ET AL: "In vivo cartilage formation from growth factor modulated articular chondrocytes." CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, (1998 JUL) (352) 239-49. , XP001015830 abstract page 240, column 1, paragraph 3 ----	1-28
E	WO 01 25402 A (TIGENIX N V ;BARI COSIMO DE (BE); LUYTEN FRANK (BE); DELL ACCIO FR) 12 April 2001 (2001-04-12) claims ----	1
Y	QUARTO, RODOLFO ET AL: "Modulation of commitment, proliferation, and differentiation of chondrogenic cells in defined culture medium" ENDOCRINOLOGY (1997), 138(11), 4966-4976 , XP001015898 abstract page 4967, column 1, paragraph 2 ----	1-28
X	VALCOURT, U. ET AL: "Different Effects of Bone Morphogenetic Proteins 2, 4, 12, and 13 on the Expression of Cartilage and Bone Markers in the MC615 Chondrocyte Cell Line" EXP. CELL RES. (1999), 251(2), 264-274 , XP001015923 abstract page 264, column 2, paragraph 1 ----	27,28
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STEWART, MATTHEW C. ET AL: "Phenotypic stability of articular chondrocytes in vitro: the effects of culture models, bone morphogenetic protein 2, an serum supplementation" retrieved from STN Database accession no. 132:203578 XP002177485 abstract & J. BONE MINER. RES. (2000), 15(1), 166-174 , -----	6-8,11, 12
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STEWART, MATTHEW C. ET AL: "Phenotypic stability of articular chondrocytes in vitro: the effects of culture models, bone morphogenetic protein 2, an serum supplementation" retrieved from STN Database accession no. 132:203578 XP002177485 abstract & J. BONE MINER. RES. (2000), 15(1), 166-174 , -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/JP 00/00118

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
US 5723331	A	03-03-1998	AU	2435495 A		29-11-1995
			WO	9530742 A1		16-11-1995
			US	5786217 A		28-07-1998
US 5902785	A	11-05-1999	AU	6024696 A		24-12-1996
			TW	422700 B		21-02-2001
			WO	9639170 A1		12-12-1996
WO 9859035	A	30-12-1998	AU	7984498 A		04-01-1999
			WO	9859035 A2		30-12-1998
WO 0125402	A	12-04-2001	AU	7634400 A		10-05-2001
			WO	0125402 A1		12-04-2001